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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/606,055 | 06/25/2003 | Charles E. Hart | 00-79D1 | 3796 |

7590 01/03/2006

Gary E. Parker
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| EXAMINER | |
|---|---|
| BORGEEST, CHRISTINA M | |
| **ART UNIT** | **PAPER NUMBER** |
| 1649 | |

DATE MAILED: 01/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/606,055 | HART ET AL. | |
| | Examiner | Art Unit | |
| | Christina Borgeest | 1649 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *31 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *25-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/28/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Election/Restrictions*

Applicant cancelled claims 1-24 by Application and Fee Transmittal form of 25 June 2003. Applicants' amendment to the claims submitted 31 October 2005 is acknowledged. Claim 25 has been amended. Applicants' election of Group IX in the reply filed on 31 October 2005 is acknowledged, and it is also acknowledged that the prior cancellation of claims 1-24 on 23 June 2003 obviates the need for an election because remaining claims 24-32 are within Group IX and recite the tissue kidney. Nevertheless, because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 25-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification does not reasonably provide enablement administration of

a humanized antibody against the protein in SEQ ID NO: 2 from amino acid residue 258 to residue 370 for reducing kidney fibrosis in a mammal.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." (See In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 Fed. Cir. 1988) These factors include, but are not limited to: (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. The claims are drawn to reducing fibroproliferative disorders of the kidney such as glomerulonephritis, diabetic nephropathy or lupus nephritis using a humanized monoclonal antibody to that binds to an epitope of a protein as shown in SEQ ID NO: 2 such as the epitope from amino acid residue 258 to amino acid residue 370. The disease and dosage are defined but the claims do not specify that the antibody is an antagonist of SEQ ID NO: 2. One skilled in the art would expect that many of the antibodies would not be antagonists; some may even be agonists.

The nature of the invention is complex, namely, the treatment of disease comprising administration of antibodies to a growth factor. Incidentally, the growth factor is known by several names in the literature, including platelet derived growth factor (PDGF)-C, spinal cord-derived growth factor (SCDGF), fallotein, (see Hamada et

al., Biochem. Biophys. Res. Comm. 2001; 280: 733-737, whole document), PDGF-D (see Appendix A—MeSH database printout) and by Applicant as zvegf4. For simplicity, examiner will use the Applicants' term, zvegf4. While the state of the art and understanding regarding molecular mechanisms of nephritis and cytokine interaction is growing (see Eitner and Floege, Curr Opin Investig Drugs. 2005; 6: 255-61, especially 256-258), the field of treatment of nephritis with cytokines is still nascent (see Coppo and Amore, Pediatr Nephrol. 2004; 19:256-65, especially p. 261, left column, 2nd paragraph). Some drugs currently being developed to treat fibrosis include anti-TNF-α, anti PDGF-β, anti-TGF-β and cytokine receptor antagonists, however, there is at best, only a general link between nephritis and cytokines (Eitner and Floege; Coppo and Amore; see pertinent page numbers above).

The predictability in the art is low. Even in cases where a nexus has been established between a specific disease and an alteration in levels of a particular protein, it cannot be predicted whether or not an effective medication can be made based on that information alone. In other words, unless a causal relationship is shown between disease status and an alteration in the levels of a particular protein, one of skill in the art cannot predict whether the protein level alteration is the cause of the disease or a side effect of the disease. For example, if levels of a particular protein change ***as a result*** of a given disease ***and are not the cause of the disease***, administering an antagonist of the protein would be ineffective in treating the disease. Therefore the skilled artisan cannot predict whether or not a new drug will be effective without empirical testing.

The amount of guidance given by the specification is insufficient. While the

specification generally asserts that antagonist antibodies of zvegf4 can be used to treat kidney fibrosis, the details of how to do this are virtually non-existent. For example, how advanced can the fibrosis be and still be treatable by the claimed method? How much does the claimed method "reduce" kidney fibrosis? How is the antibody administered (for example, systemically or locally)? What are the contraindications? Finally, Applicants provide no working examples directed to the production of antagonist zvegf4 humanized antibodies against amino acid residues 258-370 of SEQ ID NO: 2 ***or*** to the treatment of kidney fibrosis with antibodies. The quantity of experimentation required to practice the invention would be very large, considering that antagonist zvegf4 antibodies must first be made and screened, appropriate patient populations determined and all details of treatment (including dosage, administration routes, contraindications, endpoint determination) must be decided empirically.

Due to the large quantity of empirical experimentation necessary to make and screen zvegf4 antibodies, determine the appropriate patient populations and all details of treatment (including dosage, administration routes, contraindications, endpoint determination), the lack of direction/guidance presented in the specification regarding how advanced the fibrosis can be and still be treatable; how much does the claimed method "reduce" kidney fibrosis; how is the antibody to be administered and what are the contraindications, the absence of working examples directed to directed to the production of antagonist zvegf4 humanized antibodies against amino acid residues 258-370 of SEQ ID NO: 2 ***or*** to the treatment of kidney fibrosis with antibodies, the complex nature of the invention, the contradictory state and unpredictability of the prior art (Eitner

and Floege; Coppo and Amore), and the breadth of the claims which fail to recite limitations on the disease and antibodies (for instance, antagonists or agonists?) to be used in the claimed method, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

## *Conclusion*

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Borgeest whose telephone number is 571-272-4482. The examiner can normally be reached on 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Christina Borgeest, Ph.D.

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER

Pursuant to the provisions of M.P.E.P. §609 and in accordance with 37 C.F.R. §1.98(d), Applicants have not included copies of the documents listed on the 1449 forms that were previously cited by or submitted to the Patent and Trademark Office in a prior application identified herein. Below is a list of documents that were not previously cited by or submitted to the Patent and Trademark Office in any prior application identified herein. Copies of newly cited documents are provided herewith.

**List of Documents Not of Record in Prior Application**

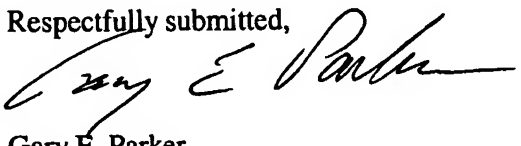
| Identifier | Applicants | U.S. Patent Number |
|---|---|---|
| A3 | Friedman, et al. | 6,264,949 |
| A9 | Rosen, et al. | WO 01/55430 |

Pursuant to the provisions of M.P.E.P. §609, Applicants further request that a copy of the 1449 form(s), marked as being considered and initialed by the Examiner, be returned with the next Official Communication.

It is believed that no fee is due, as this Information Disclosure Statement is filed prior to the receipt of any Action on the merits. However, in the event a fee is due, please charge any fee or credit any overpayment to Account No. 26-0290.

The Examiner is invited to contact the Undersigned at the below-listed telephone number, if there are any questions concerning this paper or the attached references.

Respectfully submitted,



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